Clinical Results of Extracorporeal Photopheresis

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Keywords

Extracorporeal photopheresis · ECP ·
Cutaneous T-cell lymphoma · CTCL ·
Graft-versus-host disease · Solid organ rejection

Summary

Extracorporeal photopheresis (ECP) is a combination of leukapheresis and photodynamic therapy in which blood is treated with photoactivable drugs which are then activated with ultraviolet light and re-infused to the patient. It has been used successfully for more than 30 years in the treatment of erythrodermic cutaneous T-cell lymphoma (CTCL) and over 20 years for chronic graft-versus-host disease (GVHD). ECP has also shown promising results in the treatment of acute GVHD and other T-cell-mediated diseases, including systemic sclerosis, treatment and prevention of solid organ rejection, and more recently Crohn's disease. The use of ECP may allow a significant reduction or even discontinuation of corticosteroids and/or other immunosuppressants, thus leading to reduced long-term morbidity and mortality and improved overall survival. ECP is a well-tolerated therapy. No significant side effects have been reported during the last 30 years. It has been shown that ECP is not associated with an increased incidence of infections, malignancies, or recurrence of underlying malignant disease, neither during short-term nor during long-term therapy.

Schlüsselwörter

Extrakorporale Photopherese · ECP ·
Kutanes T-Zell-Lymphom · CTCL ·
Graft-versus-Host Erkrankung · Organabstoßung

Zusammenfassung

Die extrakorporale Photopherese (ECP) ist eine Kombination aus Leukapherese und photodynamischer Therapie, bei der Blut mit photoaktiven Substanzen behandelt, mit ultraviolettem Licht bestrahlt und reinfundiert wird. Die ECP-Therapie wird seit 30 Jahren erfolgreich in der Behandlung von erythrodermen kutanen T-Zell-Lymphomen und seit 20 Jahren in der Behandlung von chronischer Graft-versus-Host-Erkrankung (GVHD) eingesetzt. Darüber hinaus konnten vielversprechende Ergebnisse in der Behandlung der akuten GVHD und anderer T-Zell-mediierter Erkrankungen einschließlich Systemischer Sklerose, Behandlung und Prävention von Abstoßungsreaktion nach Transplantation solider Organe und kürzlich auch bei Therapie des Morbus Crohn gezeigt werden. Der Einsatz von ECP erlaubt eine signifikante Reduktion oder sogar das Absetzen von Steroiden und/oder anderen immunsuppressiven Medikamenten, was zu einer Reduktion der Morbidität und Mortalität und zu einem verbesserten Gesamtüberleben führt. In den letzten 30 Jahren wurden keine signifikanten Nebenwirkungen der ECP berichtet. Es konnte gezeigt werden, dass die ECP weder bei kurzer, noch bei langer Anwendungsdauer mit einem erhöhten Risiko für das Auftreten von Infekten, Malignomen oder Rezidiv der zugrunde liegenden malignen Erkrankung vergesellschaftet ist.

Introduction

Historically, vitiligo was the first treated disorder 5,000 years ago by Egypt physicians. After ingestion of the 'ami majus plant' patients were exposed to the sunshine.

Extracorporeal photochemotherapy (ECP) was introduced in 1981 in the USA by Richard L. Edelson and initially developed for the treatment of cutaneous T-cell lymphoma (CTCL) [1]. In 1988, ECP received approval by the American Food and Drug Agency (FDA) as the first sanctioned cellular immunotherapy for cancer. After the establishment of its high efficacy in CTCL, ECP has been investigated in several other T-cell-mediated diseases, including acute and chronic graft-versus-host disease (GVHD), solid organ transplant rejection, systemic sclerosis, Crohn's disease (CD), and others. However, its mechanism of action still remains elusive. The treatment consists of two steps: a leukapheresis procedure collecting approximately 3–5% of circulating mononuclear cells and photoactivation by 8-methoxypsoralen (8-MOP) and ultraviolet A light (UVA, 1–2 J/cm²). The treated cells are then re-infused to the patient. During ECP, photoactivated 8-MOP causes cross-linking of DNA within the nuclei of lymphocytes, leading to apoptosis of these cells. The key steps of ECP are apoptosis of mononuclear white blood cells (MNC, mainly lymphocytes) after treatment with photoactivated psoralen, phagocytosis of these apoptotic cells by antigen-presenting cells (APCs), a switch in APC activity in favor of antiinflammatory cytokines and away from proinflammatory cytokines, and production of antigen-specific T-regulatory cells (T-regs) [2]. Recent clinical and animal studies have demonstrated that infusion of apoptotic cells by ECP therapy induces antigen-specific T-regs, including CD4⁺ CD25⁺ FoxP3⁺ T cells and IL-10-producing T-regs type 1. It has also been suggested that ECP therapy induces IL-10-producing regulatory B cells and regulatory CD8⁺ T cells [3]. The frequency of CD4⁺ CD25⁺ FoxP3⁺ T-regs in the peripheral blood was shown to be increased after each cycle of ECP and also during the course of treatment [4]. A therapeutic dose of treated MNCs is still under discussion. No evidence of correlation between the number of lymphocytes collected and clinical efficacy has been found, although in one study a better clinical response and faster improvement in patients receiving higher doses of MNCs was reported [5]. Two concepts of photopheresis do currently exist: a single unit apheresis device (TherakosTM Uvar XTS[®] or TherakosTM CellExTM; Therakos Inc. Exton, PA, USA) and an 'offline' system requiring three separate processing steps (leukocyte collection, addition of psoralen plus UVA (PUVA) irradiation and re-infusion of treated cells) (fig. 1). In the beginning of ECP, 8-MOP was given orally (0.5–0.6 mg/kg) prior to apheresis procedure, causing in parts substantial side effects (e.g. nausea). Since 8-MOP now is administered just to the collected MNCs (0.34 µg/ml collected cells), the total dose needed is typically only 0.25% of that used in the oral form [6]. Despite the patient has still to

Fig. 1. During ECP whole blood is drawn from the patient and separated in plasma and different cell fractions. MNCs are collected, incubated with 8-MOP, photoactivated with UVA light and re-infused to the patient.

be aware, the post-treatment risk of photosensitization could be reduced by this approach.

ECP is a well-tolerated therapy. No significant side effects have been reported, except for the short-term effects of oral 8-MOP. A reduction in red cell and platelet counts has been observed. Unlike other immunosuppressive therapies, ECP has not been associated with an increased incidence of infections or malignancies, neither during short-term nor during long-term therapy.

Extracorporeal Photochemotherapy in Dermatology

CTCLs

Cutaneous lymphomas are disorders characterized by localization of malignant lymphocytes in the skin. The majority of these lymphomas (about two thirds) are of T-cell origin and the most common form of CTCLs is mycosis fungoides (MF; about 60% of CTCL cases). Systemic therapies are used only in progressive or advanced stage of disease [7]. In contrast, Sézary syndrome (SS) is less common and accounts for only 5% of CTCL cases. The prognosis is poor, with a median survival of less than 3 years [8].

In early stages, treatment usually consists of skin-directed therapies with topical agents including corticosteroids as well as phototherapy with PUVA, where patients take 8-MOP orally followed by skin exposure to UVA light [7]. However, PUVA is associated with short-term adverse events due to

Table 1. ECP for the treatment of CTCL

Author (reference)	Year	Patients	Overall response	CR	PR
Edelson et al. [1]	1987	37	73% (27/37)	24% (9/37)	35% (13/37)
Heald et al. [52]	1989	22	86% (19/22)	23% (5/22)	45% (10/22)
Zic et al. [53]	1992	20	55% (11/20)	25% (5/20)	30% (6/20)
Prinz et al. [54]	1995	17	70% (12/17)	0% (0/17)	41% (7/17)
Gottlieb et al. [55]	1996	28	71% (20/28)	25% (7/28)	46% (13/28)
Duvic et al. [56]	1996	34	50% (17/34)	18% (6/34)	32% (11/34)
Vonderheid et al. [57]	1998	36	33% (12/36)	14% (5/36)	19% (7/36)
Zouboulis et al. [58]	1998	20	65% (13/20)	NK	NK
Jiang et al. [59]	1999	25	80% (20/25)	20% (5/25)	60% (15/25)
Bisaccia et al. [60]	2000	37	54% (20/37)	14% (5/37)	41% (15/37)
Crovetti et al. [61]	2000	30	73% (22/30)	33% (10/30)	40% (12/30)
Wollina et al. [62]	2000	20	65% (13/20)	50% (10/20)	15% (3/20)
Bouwhuis et al. [63]	2002	55	80% (44/55)	62% (34/55)	18% (10/55)
Knobler et al. [64]	2002	20	50% (10/20)	15% (3/20)	35% (7/20)
Suchin et al. [65]	2002	47	79% (37/47)	26% (12/47)	53% (25/47)
Quaglino et al. [66]	2004	19	63% (12/19)	NK	NK
Richardson et al. [67]	2006	28	89% (25/28)	29% (8/28)	61% (17/28)

CR = Complete response; PR = partial response (>50% improvement in skin scores);
NK = not known.

psoralen intake (e.g. nausea, vomiting) and long-term complications such as photosensitivity and the potential for the development of skin cancer. Since the publication of the first multicenter trial of ECP by Edelson in 1987 reporting responses in 27/37 (73%) of patients with advanced refractory CTCL, data on >1,000 patients with CTCL treated with ECP have been reported from worldwide centers [9]. The European Organization for Research and Treatment of Cancer (EORTC) recently published European consensus recommendations for the treatment of MF/SS based on available evidence and best practices from each national group [7]. ECP is recommended as a first-line therapy for both erythrodermic MF and SS. The standard schedule for ECP in the treatment of CTCL consists of procedures performed on 2 consecutive days every 2–4 weeks, which is generally continued for up to 6 months to assess response. Maintenance therapy may be tailored according to disease response and severity. It was also noted that the response rate to ECP may be increased with the addition of immunomodulatory therapy such as IFN- α [7]. Response rates to ECP have been shown to vary widely between different study groups, from 43 to 100% [10]. A summary of the largest studies publishing response rates using ECP for the treatment of CTCL is provided in table 1. The differences in response rates between centers may relate to different patient selection for treatment with ECP such as the presence of a peripheral T-cell clone, stage of disease, prior treatment, ECP protocol, duration of ECP, and definition of response [10].

One major consequence of ECP in CTCL is the induction of apoptosis resulting from the fact that 8-MOP binds covalently to DNA in the separated leukocytes, leading to cell cycle arrest and apoptosis after UVA irradiation. The phago-

cytosis of apoptotic leukocytes by antigen-presenting cells and impaired function of other dying cells induce several changes in the immune response through many different actors such as dendritic cells, regulatory cells and cytokine pattern modifications.

Systemic Sclerosis

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder of unknown etiology characterized by abnormal excessive deposition of collagen and obliterative vasculopathy in the skin and visceral organs, such as the kidneys, heart, lungs, and gastrointestinal tract. Patients with severe, progressive SSc have a relatively poor prognosis with a 10-year survival rate of about 20% [11].

In a randomized, single-blind, controlled trial including 79 patients, ECP was shown to induce a significant improvement in skin severity scores and mean percentage of skin involvement when compared with a control group of patients only receiving D-penicillamine treatment. After 6 months of treatment, a statistically significant reduction in skin severity scores was observed in 68% of patients receiving ECP as compared with 32% of patients on a regimen of D-penicillamine [12].

Subsequently, a randomized, double-blind, placebo-controlled trial conducted at 16 investigational sites in the USA, Canada, and Europe was initiated by Knobler et al. [13]. Patients were randomized at baseline to receive either active or sham ECP according to a secure computer-generated randomization schedule. Treatment was performed on 2 consecutive days every 4 weeks for 12 months. Severity of skin (skin scores assessed in 22 body regions) and joint involvement (60 joints examined for contractures) were assessed on a monthly basis. A statistically significant improvement in skin scores as

compared with baseline was observed at 6 months and 12 months among patients who received active ECP, but not among patients who received sham ECP. Comparison of skin scores between the two study arms did not achieve statistical significance because of the small sample size of the study arms. Joint involvement was also significantly improved after 6 months and 12 months of active ECP when compared with baseline [13]. Based on the available literature, especially patients with early stage of disease and significant skin involvement seem to respond best to ECP. However, only long-term treatment leads to continuous improvement in SSs patients.

Extracorporeal Photochemotherapy in Transplantation

Acute GVHD

Acute GVHD is a frequent complication of allogeneic hematopoietic stem cell transplantation (HCT) that occurs in approximately 60% of HLA-identical sibling transplants [14] and up to 80% of matched unrelated donor transplants [15] and contributes substantially to post-transplantation morbidity and mortality. HLA disparity, patient and donor age and gender, dose and source of hematopoietic stem cells, intensity of conditioning regimen and GVHD prophylaxis can influence development of GVHD [14, 16, 17]. After myeloablative conditioning regimens, acute GVHD occurs within 2–4 weeks after HCT, whereas after reduced-intensity conditioning the onset of acute GVHD may be delayed until 2–3 months after HCT. Recently, the National Institutes of Health (NIH) Consensus Development Project distinguished classic acute GVHD presenting within 100 days of HCT with acute GVHD features from persistent, recurrent, or late-onset acute GVHD occurring beyond 100 days of HCT or donor lymphocyte infusion (DLI) [18].

The major target organs affected by acute GVHD are skin, liver, and gastrointestinal tract. Skin manifestations consist of maculopapular rash, erythrodermia, bullae formation, and epidermal separation similar to toxic epidermal necrolysis. Liver GVHD manifests with hyperbilirubinemia as well as increased alkaline phosphatase and transaminase levels. Gastrointestinal involvement is characterized by diarrhea and in some patients by persistent nausea. Criteria for grading acute GVHD were published in 1974 by Glucksberg and colleagues [19].

The established first-line therapy for treatment of acute GVHD consists of corticosteroids since more than 25 years [20]. However, only 24% of patients after unrelated HCT and about 40% of patients after related HCT respond to this approach [20, 21]. Non-responding patients require additional immunosuppressive therapy (e.g. poly- or monoclonal antibodies, immunotoxins, other immunosuppressive interventions) are at high risk for additional morbidity and mortality due to life-threatening infections, including invasive fungal, bacterial and viral infections or organ failure.

Fig. 2. Kaplan-Meier probability of overall survival among patients with steroid-refractory and -dependent acute GVHD was significantly higher among those showing complete response (CR) to ECP (black line) compared with those with no CR to ECP (grey line).

This figure was published in Greinix, et al: The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. *Haematologica* 2006;91:405–408, Copyright © 2006 Ferrata Storti Foundation.

After promising results of early studies with ECP in patients with steroid-refractory GVHD [22, 23], a pilot study in 21 steroid-refractory patients was initiated, showing an overall complete response rate of 60% after 3 months of ECP [24]. Subsequently, a prospective phase II study was performed by Greinix et al. [25] with the so far largest treated cohort, including 37 steroid-refractory and 22 steroid-dependent GVHD patients. Patients underwent ECP on 2 days a week (= one cycle) in weekly intervals until maximal response was achieved. Then, ECP was stopped without maintenance therapy. A complete resolution of acute GVHD was achieved in 82% of patients with skin, in 61% with liver, and in 61% with gut transplants after a median of 4 cycles of ECP, during a median of 1.3 months of therapy. Complete response rates were higher for patients with grade II and III disease (86% and 55%, respectively) than for grade IV disease (30%). Using an intensified ECP schedule with two treatments on a weekly basis, response rates in grade IV disease and gut involvement could be improved significantly compared to the pilot study [24]. ECP allowed accelerated tapering of corticosteroids and their discontinuation in responders after a median of 55 days, which had a positive effect on transplantation-related mortality. The probability of overall survival projected at 4 years was significantly higher for patients who achieved a complete response to ECP (59% vs. 11%), compared with those who did not (fig. 2). These long-term results demonstrated that the effects of ECP in patients with acute GVHD were durable and improved overall survival. The most impor-

Table 2. ECP in patients with steroid-refractory acute GVHD

Author (reference)	Year	Patients	CR/PR skin, %	CR/PR liver, %	CR/PR gut, %	Overall survival, %
Greinix et al. [23]	1998	6	100	100		100
Greinix et al. [24]	2000	21	81	67	0	57
Salvaneschi et al. [68]	2001	9	89	20	60	67
Dall'Amico et al. [69]	2002	14	79	57	70	57
Messina et al. [34]	2003	33	82	60	75	69
Garban et al. [70]	2005	12	67	0	40	42
Greinix et al. [25]	2006	59	93	65	74	59
Kanold et al. [71]	2007	12	100	67	83	75
Perfetti et al. [72]	2008	23	66	27	40	48
Calore et al. [73]	2008	15	92	100	71	85
Perotti et al. [74]	2010	50	83	67	73	64

CR = Complete response; PR = partial response (>50% improvement in organ involvement).

Fig. 3. Cumulative incidence of complete or partial response of skin was higher among patients with steroid-refractory/-dependent/-intolerant chronic GVHD treated with ECP than in the control group. This figure was originally published in Flowers et al: A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood* 2008;112:2593–2594. Copyright © 2008 The American Society of Hematology.

tant findings in ECP treatment of patients with acute GVHD are that ECP is steroid-sparing, does not impair the graft-versus-leukemia effect, and does not increase the risk for opportunistic infections. Since neither increased rates of infections nor recurrence of underlying malignant disease have been observed during ECP [24], this promising treatment is unlikely to induce a generalized immunosuppression. Table 2 summarizes the main published results on the use of ECP in patients with acute GVHD who failed steroid first-line therapy.

Chronic GVHD

Chronic GVHD affects 30–80% of HCT recipients depending on patient age, donor type, stem cell source, graft manipulation, and the use of DLI [26–28]. It is a multiorgan autoim-

mune-like syndrome similar to other immunologic disorders such as scleroderma, Sjögren syndrome, primary biliary cirrhosis, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency. Severe chronic GVHD has a major influence on late morbidity and mortality after HCT; if untreated, fewer than 20% of patients survive without disability at 4 years after HCT [29, 30]. Lower survival rates, higher non-relapse mortality and longer duration of systemic immunosuppressive therapy are reported in patients with high-risk features of chronic GVHD like platelet counts $< 100 \times 10^9/l$ or progressive onset of chronic GVHD [31].

The classification of chronic GVHD as to be ‘limited’ or ‘extensive’ was based on results of a small retrospective study performed in 1980 [32]. The NIH Consensus Development Project on Criteria for Clinical Trials in chronic GVHD developed recently standardized criteria for diagnosis of chronic GVHD and a new scoring system for describing the extent and severity of chronic GVHD [18].

Again, corticosteroids represent a major treatment component. However, therapy of chronic GVHD should begin as soon as possible after initial diagnosis to improve the long-term outcome of patients. Overall survival at 3 years is reported to be 76% if corticosteroids are started early compared to only 23% if started late in the course of disease [30, 33].

During the last years a remarkable number of patients has been treated with ECP for steroid-refractory chronic GVHD, high response rates have been reported in cutaneous and visceral manifestations [23, 34]. Patients with severe sclerodermatous chronic GVHD had a clear benefit from longer treatment duration [23, 25]. Several retrospective studies demonstrated the efficacy of ECP for patients with chronic GVHD, but no association between treatment intensity (number of ECP procedures per month) and clinical response could be found [25]. Responses to ECP appear to be more frequent in patients treated earlier (less than 9 months) after diagnosis of chronic GVHD, a steroid-sparing effect could be demonstrated, and in the majority of responders other immunosuppressants could be discontinued [34, 35]. Messina and col-

Table 3. ECP in patients with steroid-refractory chronic GVHD

Author (reference)	Year	Patients	ORR (%)	Survival
Greinix et al. [23]	1998	15	8 CR, 6 PR (93)	14/15 (93%) at 15 mo
Smith et al. [75]	1998	18	3 CR, 3 PR (33)	7/18 (39%) at 2 y
Salvaneschi et al. [68]	2001	14	4 CR, 5 PR (64)	11/14 (79%) at 3 y
Messina et al. [34]	2003	44	15 CR, 10 PR (68)	34/44 (77%)
Seaton et al. [76]	2003	28	10 PR (36)	24/28 (86%)
Apisarnthanarax et al. [77]	2003	32	7 CR, 11 PR (56)	19/32 (59%)
Foss et al. [78]	2005	25	16 PR (64)	15/25 (60%)
Rubegni et al. [79]	2005	32	9 CR, 13 PR (69)	
Couriel et al. [35]	2006	71	14 CR, 29 PR (61)	13/71 (18%) at 5 y
Greinix et al. [25]	2006	47	23 CR, 16 PR (83)	42/47 (89%)
Perseghin et al. [80]	2007	25	11 CR, 9 PR (80)	19/25 (76%) at 2 y
ORR = Overall response rate; CR = complete response; PR = partial response; mo = months; y = years.				

leagues [34] observed a significantly higher 5-year overall survival rate (96% vs. 58%) in patients responding to ECP compared to non-responders. Recently, results of a multicenter, prospective, randomized, phase II study in 95 patients with steroid-refractory, steroid-dependent, or steroid-intolerant chronic GVHD were published. Patients were randomized either to conventional treatment with steroids plus calcineurin inhibitors or to conventional treatment plus ECP for 24 weeks [36]. Patients were treated with ECP 3 times during week 1, then twice weekly during weeks 2–12, and responding patients could continue 2 ECP treatments every 4 weeks until week 24. Numerically greater improvements in total skin score (TSS) were observed with ECP plus conventional treatment than with conventional treatment alone although the difference was not statistically significant. However, ECP led to significantly higher complete response and partial response (40% compared to 10%), and the proportion of patients who had at least a 50% reduction in steroid dose and at least a 25% decrease from baseline in the TSS was 8.3% at week 12 compared to 0% with conventional therapy alone.

Table 3 summarizes the main published results on the use of ECP in patients with chronic GVHD.

Solid Organ Transplant Rejection

Early, small pilot studies in patients with cardiac transplant rejection indicated that ECP in addition to conventional immunosuppressive treatment could reduce or reverse rejection and reduce the incidence of rejection episodes [37, 38]. Subsequently, larger studies followed to investigate the prophylactic use of ECP in this setting [39]. A phase II study analyzed the impact of ECP given or not given in addition to conventional immunosuppression within 30 h of primary cardiac transplantation in 61 patients. The ECP group had a significant reduction of acute rejection episodes compared to standard therapy alone (61% vs. 81%) [40].

In lung transplant recipients the development of bronchiolitis obliterans syndrome (BOS) – a form of chronic allograft rejection – remains a major complication [41]. A retrospective

analysis of 14 patients with BOS demonstrated the benefit of ECP in reversing acute rejection and treating low-grade BOS [42]. Overall, data of approximately 50 patients receiving ECP after lung transplantation are available in the literature. ECP seems to be very effective to treat acute rejection: ECP treatment was successful in 14 of 16 published cases. With regard to BOS, 12 of 45 patients improved and 16 of 45 remained stable. These patients, however, were already resistant to other therapies and had advanced disease.

Case reports and small studies have also demonstrated the benefit of ECP in the management of liver and renal transplant rejection or as rejection prophylaxis. Urbani et al. [43] showed reversal of graft rejection after hepatic transplantation in 5 patients; in 3 of them immunosuppressants could be reduced. Additional studies have been performed using ECP for prophylaxis of allograft rejection in case of delayed introduction of calcineurin inhibitors (CNI) among high-risk liver transplant recipients to avoid CNI toxicity. Another approach is the use of ECP for prevention of acute cellular rejection among ABO-incompatible liver transplant recipients, where none of the reported 11 patients treated with ECP developed a cell-mediated rejection [44]. In patients with renal allograft rejection, small studies could show that ECP was able to reverse rejection in patients who were refractory to conventional treatment and led to improved or stable graft function [45–47]. However, controlled studies with larger patient numbers are needed to confirm these findings in liver and renal transplant.

ECP in CD

CD is a progressive, relapsing, T-cell-mediated inflammatory disorder, treated with systemic steroids and salicylate or, in more advanced stages, in combination with immunomodulators and/or TNF- α antagonists. Small preliminary studies evaluating the impact of ECP showed that a discontinuation or marked reduction of steroid dose could be achieved in treated patients. However, long duration of refractory CD leads to less well responses, suggesting an early use in patients with steroid-

Table 4. Clinical applications of ECP therapy

Disease	ASFA category
CTCL (including SS)	
Erythrodermic	I
Non-erythrodermic	III
GVHD	
Skin (acute and chronic)	II
Non-skin (acute and chronic)	III
Heart transplant	
Prophylaxis	I
Rejection	II
Lung transplant rejection	II
Liver transplant rejection	not rated
Kidney transplant rejection	not rated
Scleroderma (progressive SSc)	IV
Pemphigus vulgaris	III
CD	not rated

ASFA = American Society for Apheresis

dependent disease [48, 49]. In a recent multicenter study including 28 patients with moderate to severe CD refractory to immunomodulators and/or TNF- α antagonists, ECP treatment achieved a marked reduction in CD activity: 50% of patients responded and 25% were in remission [50].

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Conclusion

According to the literature published thus far, ECP is an established first-line therapy in CTCL. In other severe and difficult-to-treat circumstances, such as acute and chronic GVHD, SSc or allograft rejection, ECP has shown improved efficacy. Guidelines on the use of therapeutic apheresis in clinical practice have been established from the Apheresis Applications Committee of the American Society for Apheresis (ASFA guidelines) and are shown in table 4 [51]. As ECP treatment allows to reduce the dosage of corticosteroids and other immunosuppressive drugs, reduced long-term morbidity and mortality in responding patients has been reported.

The data collected during the last 25 years of the use of ECP demonstrated that the procedure is tolerated well, with no clinically significant side effects.

Disclosure Statement

The authors declare that they have no competing interests.

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